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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,804	09/12/2003	Gerold Schuler	1430/16	8361

25297 7590 05/22/2009

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EXAMINER	
JUEDES, AMY E	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
05/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,804	SCHULER ET AL.	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 24-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 24-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of this application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Amy E. Juedes, Group Art Unit 1644, Technology Center 1600.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 3/2/09 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/2/09 has been entered.

Claims 12, 24-25, and 28-32 have been amended.

Claim 33 has been added.

Claims 12 and 24-33 are pending and are under examination.

3. Upon reconsideration, the rejection of the claims under 35 U.S.C. 103 is withdrawn.

4. The following are new grounds of rejection.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 25-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, there is insufficient written

description to demonstrate that applicant was in possession of the claimed genus of "ligands" that specifically bind to CD4, CD25, or CTLA-4.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

The instant claims are drawn to a method employing a "ligand" that specifically binds to CD4, CD25, or CTLA-4 that can be used to remove CD4+CD25+ regulatory T cells from blood. The instant specification on page 7 discloses that "ligands" relate to all kinds of compounds capable of binding to specific molecules. Thus, the claims encompass a broad range of structurally different molecules, including peptides, proteins, antibodies, small molecules, lipids, etc. While antibodies for cell surface receptors such as CD4, CD25, or CTLA-4 are well known in the art and are conventionally used to separate (i.e. remove) cells expressing the receptors, there is no evidence that other types of ligands that perform the function of the claims are well known in the art. Additionally, the specification does not disclose a correlation between the structure and function of the ligands as broadly claimed. Furthermore, the specification only discloses a single species of "ligand", CD4, CD25, or CTLA-4 specific antibodies. This is not sufficiently representative of the broad range of structurally different "ligands" encompassed by the claims. Thus, one of skill in the art would conclude that the specification fails to provide adequate written description to demonstrate that Applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 24-29, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Koulis et al., February 2001, as evidenced by Miltenyi Biotec product information, 2007.

Koulis et al. teach a method for isolating (i.e. removing) CD4+CD25+ regulatory T cells from human peripheral blood comprising separating CD25+ populations from human PBMC using microbeads and a MACS column. As evidenced by Miltenyi Biotec product information, microbeads used in MACS technology for enrichment of CD25+ cells comprise a microbead conjugated to an anti-CD25 antibody. Thus, the method of enriching CD25+ cells of Koulis et al. inherently comprises contacting the PBMCs with a CD25 antibody conjugated to a microbead. Koulis et al. further teach testing the isolated CD4+CD25+ cells for regulatory activity. Koulis et al. teach that the CD4+CD25+ regulatory T cells exhibit diminished proliferation to anti-CD3/CD28 (i.e. are in an anergic state or are non-proliferative following stimulation with a TCR stimulating agent). Koulis et al. also teach that activated CD4+CD25+ T cells suppress the proliferation of T cells in a co-culture experiment in a cytokine independent manner. Additionally, the starting PBMC population of Koulis et al. comprises CD4+ T cells and has been isolated from total peripheral blood. Therefore, said PBMCs are an isolated population of cells comprising CD4+ T cells. Thus, Koulis et al. have isolated a population of CD4+CD25+ T cells from a population of CD4+ T cells, as recited in claim 33.

Thus, the reference clearly anticipates the invention.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art

> are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, 24-30, and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koulis et al., February 2001, in view of Thornton et al., 1998.

The teachings of Koulis et al. are described above.

Koulis et al. do not teach determining whether the suppression of T cell proliferation is contact dependent, nor determining the cytokine profile of the regulatory T cells.

Thornton et al. teach that CD4+CD25+ regulatory T cells from mouse produce IL-10, but not IL-2, IL-4, or IFN-gamma (see page 290, in particular). Thornton et al. also teach that said mouse regulatory T cells suppress the proliferation of CD4+ T cells in a contact dependent and cytokine independent manner (see page 290 in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test the human regulatory T cells of Koulis et al., for contact dependent regulatory function and production of cytokines, as taught by Thornton et al. The ordinary artisan would have been motivated to test the human regulatory T cells of Koulis et al. in assays taught by Thornton et al. for mouse regulatory T cells, since Koulis et al. teach that the human CD4+CD25+ regulatory T cells are analogous to the CD4+CD25+ regulatory T cells in mice. Furthermore, the ordinary artisan would have had a reasonable expectation of success in determining that the human regulatory CD4+CD25+ exhibit the same properties as the mouse

CD4+CD25+ T cells, since Koulis et al. teach that human CD4+CD25+ regulatory T cells are hyporesponsive to CD3 stimulation and suppress T cell proliferation after activation in a cytokine independent manner (i.e. exhibit identical properties to the analogous mouse CD4+CD25+ regulatory T cells of Thornton t al.). Thus, testing the various regulatory properties of the human CD4+CD25+ regulatory T cells involves choosing among a finite number of predictable options which could be pursued with a reasonable expectation of success. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense (see *KSR International Co. V. Telefex Inc* 82 USPQ2d 1385).

8. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koulis et al., February 2001 and Thornton et al., 1998, as applied to claims 12, 24-30, and 32-33 above, and further in view of Stout et al., 1993.

The combined teachings of Koulis et al. and Thornton et al. are discussed above.

They do not teach testing the regulatory properties of CD4+CD25+ regulatory T cells using CD4+CD25+ T cells that have been fixed.

Stout et al. teach that T cells effector functions that are contact dependent, but not cytokine dependent, can be mediated even when the T cells are fixed after activation.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Stout et al. to the methods of testing regulatory function of the CD4+CD25+ T cells made obvious by Koulis et al. and Thornton et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do so, since Koulis et al. and Thornton et al. teach that activated CD4+CD25+ regulatory T cells function via a cytokine independent, contact dependent mechanism, and Stout et al. teach that contact dependent, cytokine independent T cell functions can be performed even after fixation of the activated T cells.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 7am to 3:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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